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Original article

Surgical treatment of pancreatic adenocarcinoma using cephalic duodenopancreatectomy (Part 2). Long term follow up after 204 cases

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ABSTRACT

Introduction: Surgery is the accepted treatment in adenocarcinoma of the head of the pancreas (ADHP); however, the long-term survival continues to be low. The aim of this study is to define prognostic factors of long-term survival after cephalic duodenopancreatectomy (CDP) due to pancreatic adenocarcinoma.

Material and methods: We have collected data on the treatment of adenocarcinoma of the head of the pancreas by means of a cephalic duodenopancreatectomy performed at the Hospital Universitari de Bellvitge (Barcelona) from 1991 to 2007.

Results: A total of 204 CDP due to ADHP were performed. The histology showed that the resected tumour was larger than 3cm in 70 cases, with lymphatic infiltration in 73%, perineural invasion in 89%, and lymphatic involvement in 89%. More than 15 lymph nodes were resected in 120 patients. A total of 113 (60%) patients received adjuvant treatment after surgery. There were 148 (73%) deaths, of which 55 (27%) were alive at closure. The actual mean survival was 2.54 years (95% CI; 2.02-3.07) and an actuarial survival at 5 years of 13.55% (95% CI; 7.69-19.41).

The study of mortality risk factors showed that, female gender, absence of peri-operative transfusion (*P*=.003), the resection of more than 15 lymph nodes during the operation (*P*=.004), and the administration of adjuvant treatment (*P*=.004) had a better long-term prognosis. The multivariate analysis showed that transfusion and gender were the most significant variables.

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Conclusions: Surgery of head of the pancreas adenocarcinoma must include an adequate lymphadenectomy, and must be performed with a low morbidity and without the need of a peri-operative transfusion.

Tratamiento quirúrgico del adenocarcinoma pancreático mediante duodenopancreatectomía cefálica (parte 2). Seguimiento a largo plazo tras 204 casos

Palabras clave:
Cáncer de páncreas
Adenocarcinoma pancreático
Duodenopancreatectomía cefálica
Cirugía oncológica del páncreas
Supervivencia a largo plazo

RESUMEN

Objetivo: Definir factores pronóstico de supervivencia a largo plazo tras la duodenopancreatectomía cefálica por adenocarcinoma pancreático.

Introducción: La cirugía es el tratamiento aceptado en el adenocarcinoma de páncreas cefálico, sin embargo la supervivencia a largo plazo sigue siendo baja.

Material y métodos: Hemos recogido la experiencia en el tratamiento del adenocarcinoma de cabeza de páncreas (ADCP) en el Hospital Universitari de Bellvitge mediante duodenopancreatectomía cefálica (DPC) desde 1991 hasta 2007.

Resultados: Se realizaron 204 DPC por ADCP. El estudio histológico evidenció que el tumor resecado tenía un tamaño superior a 3 cm en 70, con permeación linfática en un 73%, invasión perineural en 89% y afectación linfática en 71%. En 120 pacientes se resecaron más de 15 adenopatías. Tras la cirugía, se administró tratamiento adyuvante a 113 pacientes (60%). Se contabilizaron 148 fallecimientos (73%), estando vivos al cierre del mismo 55 (27%). La supervivencia actual media fue de 2,54 años (IC 95% 2,02-3,07) y la supervivencia actuarial a 5 años de 13,55% (IC 95% 7,69-19,41).

El estudio de factores de riesgo de mortalidad reveló que el sexo femenino (p = 0,005), la ausencia de transfusión perioperatoria (p = 0,003), la resección de más de 15 adenopatías en la intervención (p = 0,004) y la administración de tratamiento adyuvante (p = 0,004) comportaron mejor pronóstico a largo plazo. El estudio multivariante demostró que transfusión y sexo fueron las variables de interés.

Conclusiones: La cirugía del adenocarcinoma de cabeza de páncreas debe incluir una linfadenectomía suficiente y debe realizarse con baja morbilidad y sin necesidad de transfusión perioperatoria.

Introduction

Pancreatic cancer continues to be a major health problem, and is the fourth highest cause of cancer-related death, affecting 8-10 people per 100 000 inhabitants per year.[1,2] Alarmingly, the incidence of the disease is very similar to the yearly mortality rate, in other words, the number of new patients per year is similar to the number of deaths. As is shown, pancreatic cancer survival is low, ranging between 0.4% and 4% after 5 years, according to study.[3,4] It is currently accepted that surgical resection increases survival in patients with localised disease, but only 10%-20% of patients would be able to undergo operation at the time of diagnosis.[5] Meanwhile, although adjuvant treatment appears to increase patient survival,[6-8] the treatment scheme still lacks standardisation, and its benefits are under discussion.[9-13] The objective of this study is to review the results obtained at our institution for surgically treating cancer of the head of the pancreas and to define the variables that influence long-term survival.

Material and method

We have analysed the experience gained in treating adenocarcinoma of the head of the pancreas (ADHP) at the *Hospital Universitari de Bellvitge* (Bellvitge University Hospital) using cephalic duodenopancreatectomy (CDP) between 1991 and 2007. We have created a prospective registry of the demographical, histopathological, and follow-up data from all of them.

Preoperative examination

Given the length of the study, the CT technique was modified partway through. Between 1991 and 1994, a non-helical CT scan was used. Between 1994 and 2004, a single-slice helical CT scan was used. Since 2003, multidetector CT scans have been used with 4-, 16-, and later 64-slices. Preoperative biliary drainage is not a universal practice,[6] and is only indicated in those patients that present doubts regarding final patient

care or whose surgery is expected to be delayed more than 15 days. Neither the advanced age of the patient nor the size of the tumour have been considered contraindications for the procedure.

Non-resectability criteria include the presence of metastasis, arterial invasion (superior mesenteric artery, hepatic artery, or celiac trunk) venous obliteration, or invasion of other contiguous organs (except the duodenum).[7] The definition of arterial invasion is the presence of direct contact between the tumour and the arterial vessel, even when below 50%. Regarding venous involvement, invasion is considered to be any contact greater than 50% between the tumour and the vessel, and obliterations of any segment of the portal-mesenteric venous axis are considered unresectable.[14-17] All other venous parietal involvement is considered apt for resection. Distant adenopathies have also contraindicated surgical resection.[18,19] A fresh sample analysis was needed at the before the intervention and if pathological pre aorto-caval adenopathies were present, resection was contraindicated.[20-23]

Surgical technique and histopathological study

The technique used in all cases was a standard lymphadenectomy (peripancreatic and periduodenal lymph node tissue) that was extended to the hepatic hilum, the right border of the superior mesenteric artery, and the pre aorto-caval region (Figure 1).[24,25] In order to simplify the study of the regions of lymph node involvement, we defined the peripancreatic region as the local territory (loc), and the inter aorto-caval region as the regional territory (reg).[18,26-30]

The same pathologist performed the histopathological studies in all cases, and especially focused on the pathology. A strict protocol was followed for this sample in terms of the borders of resection, with analysis of the retroperitoneal margin[31,32] and the border of the section of the pancreatic neck, as well as an analysis of the lymph node territories.[33] During the intervention, a section of the pancreatic neck was sent for a fresh sample analysis. The involvement observed in this section meant that the pancreatectomy had to be extended, and another analysis and third resection or a total duodenopancreatectomy performed if the disease persisted.[34]

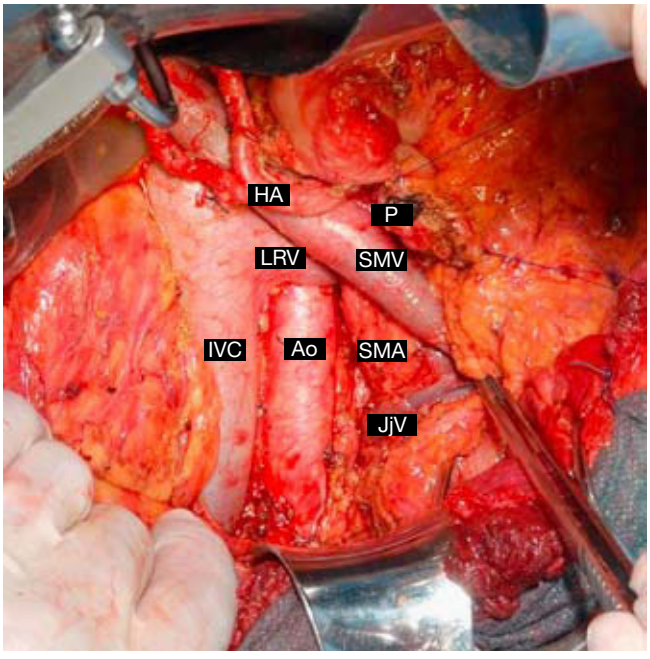

Figure 1 – Detail of a jejunal vein and interaortocaval lymphadenectomy. Ao, aorta; HA, hepatic artery; IVC, inferior vena cava; JjV, jejunal vein; LRV, left renal vein; P, section of the neck of the pancreas; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Adjuvant treatment

Adjuvant treatment was indicated in patients with poor prognosis factors, i.e. those as the presence of tumours with involved adenopathies, perineural invasion, vascular invasion, and venous invasion. The patients received a regimen based on 5-FU in a continuous infusion for 5 days during the 1st and 4th weeks of radiotherapy. Radiotherapy was administered until reaching dosages between 50.4 and 59.4 Grays (Gy), depending on the level of involvement within the surgical margins.[10]

Statistical analysis

We performed a descriptive statistical analysis based on measures of central tendency (mean, median) and variation (standard deviation and interquartile range) according to the criteria for normality (Kolmogorov-Smirnov test). We then performed a comparative study between qualitative variables using chi-square and Fisher's exact tests, and quantitative variables using the Student's t-test and Mann-Whitney U test. We also performed a Kaplan Meier analysis to determine global survival and its predictive variables, and those variables that had a statistically significant association in the logrank test ($P<.05$) with no interaction between them were considered in a Cox regression model. The goodness of fit of the previously mentioned multivariate models were analysed according to Hosmer-Lemeshow and the Area Under the Curve (AUC). We used SPSS software version 12.0®, and P values <.05 were considered to be statistically significant in all cases.

Results

Demographical details

During the period from 1991 to 2007, 204 CDP were performed at our institution for ADHP. Regarding the demographical data, the patients were older than 70 years in 57 cases (28%), and the majority were male (62%) (Table 1).

CDPPP: cephalic duodenopancreatectomy with pyloric preservation; CDPW: cephalic duodenopancreatectomy with

Table 1 – Characteristics of patients operated on for pancreatic adenocarcinoma using cephalic duodenopancreatectomy. Hospital Universitari de Bellvitge, 1991-2007

Variables	No.	%	No.	%
Sex (male/female)	127	62	77	38
Age (<70/>70 years)	147	72	57	28
A.S.A. (I-II/III)	138	69	62	31
ERCP (yes/no)	43	21	158	79
Surgical technique (CDPW-CDPWR2-CDPPP-TP), No./%	119 58	11 5	66 33	8 4
Venous resection (yes/no)	35	17	169	83
Complications (yes/no)	91	45	112	55
Surgical reintervention	14	7	120	70
Postoperative mortality (yes/no)	14	7	190	93
Transfusion during the first 48 h (yes/no)	141	72	53	28
Tumour size (<30 mm/>30 mm)	134	65	70	35
Invaded lymph territory (loc/reg/loc-reg) (No./%)	109 77	3 2	30 21	
No. resected adenopathies (≤15/>15)	75	39	120	61
Lymphatic permeation (yes/no)	139	73	52	27
Perineural invasion (yes/no)	154	89	19	11
Vascular invasion (yes/no)	74	40	114	60
Degree of tumour differentiation (mild/mod/sev), No./%	11 7	129	76 29	17
Tumourous lymph nodes (yes/no)	145	71	58	29
Synchronous metastases (yes/no)	11	60	190	94
Invasion of resection margins (yes/no)	36	18	167	82
Invasion of the retroperitoneal margins (mesouncinate) (yes/no)	7	4	186	96
Invasion of the neck of the pancreas (yes/no)	11	6	183	94
Adjuvant treatment (yes/no)	113	60	77	40
Current state (alive/dead)	55	27	148	73

CDPPP indicates cephalic duodenopancreatectomy with pyloric preservation; CDPW, cephalic duodenopancreatectomy with gastrectomy; CDPWR2, cephalic duodenopancreatectomy with gastrectomy and lymphadenectomy extended to the celiac trunk and superior mesenteric artery; TP,total pancreatectomy.

gastrectomy; CDPWR2: cephalic duodenopancreatectomy with gastrectomy and lymphadenectomy extended to the celiac trunk and superior mesenteric artery; loc: local; loc-reg: local and regional; mild: mild; mod: moderate; TP: total pancreatectomy; reg: regional; sev: severe.

Surgical technique and histopathological study

The most frequently used surgical technique was resection of the head of the pancreas with gastrectomy, used in 58% of cases (CPDW), and pyloric preservation (CDPPP) used in 66 cases (33%). Thirty-five patients (17%) underwent a resection of the portal vein or the superior mesenteric vein. Furthermore, involvement of the borders required a total pancreatectomy (TP) in 8 cases (4%). At the beginning of the study, an extended lymphadenectomy (CDPWR2, adenopathy resection in the territories of the celiac trunk and the left side of the Superior Mesenteric Artery) was performed on 11 patients (5%), a technique that was later abandoned due to the high rate of morbidity (Table 1).

The histological study showed that the resected tumour was larger than 3cm in 70 cases (35%) with a median size of 29 mm (range: 10-75 mm). We defined two different patient groups according to the number of adenopathies resected: those with 15 nodes or less (76/38%) and over 15 nodes (120/62%). The mean number of nodes resected in each patient according to the group was 10.1 vs 25 (P<.001).

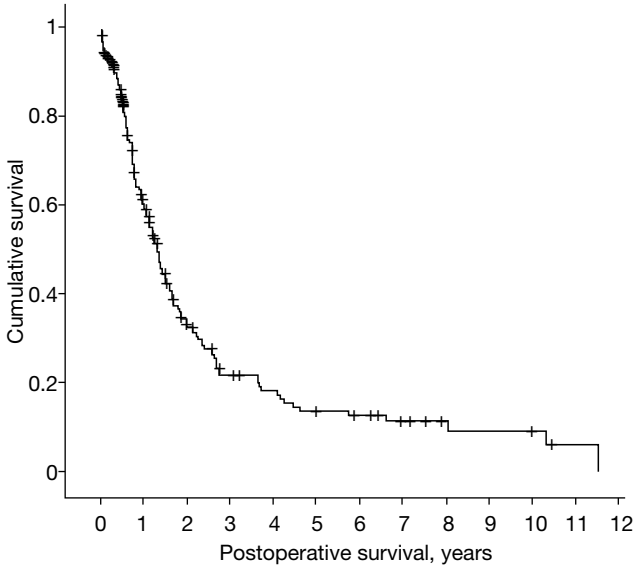

Figure 2 – Actuarial survival following cephalic duodenopancreatectomy for pancreatic adenocarcinoma. Hospital Universitari de Bellvitge, 1991-2007.

The mean number of affected lymph nodes per patient was 1.7 vs 3.2 (P=.001) with a ratio of affected nodes/resected nodes of 0.17 vs 0.13 (P=.05). As such, the ratio of affected/

resected nodes was greater in those patients that underwent resections of only a few nodes. Lymph node involvement (pN1) was similar between patients with more than 15 nodes resected and those with less than 15. A total of 51/76 (67%) patients had lymph node involvement in the group of less than 15 adenopathies resected, and 90/120 (75%) in the group with more than 15 adenopathies (n.s.). Nor were there any differences observed when comparing groups by the lymph node territory that underwent resection (local or regional).

Tumours had pathological signs with poor prognoses in the majority of cases, such as lymphatic permeation (73%), perineural invasion (89%), and lymph involvement (71%). Furthermore, doubtful signs of distant involvement were found in 11 patients (6%), with a negative perioperative result. Lastly, involvement of the resected borders was detected in 36 patients (18%) (Table 1).

Long-term follow-up

After surgery, patients were referred to the medical and radiotherapy oncology departments, with adjuvant treatment administered in 113 patients (60%). During the follow-up period, 148 patients died (73%), and 55 patients survived until the end of the period (27%). The mean patient survival was 2.54 years (95% CI: 2.02-3.07), and the median was 1.33 years (95% CI: 1.15-1.51); actuarial survival at one year was 60%, 21% at 3 years, and 13.55% at 5 years (95% CI: 7.69-19.41) (Figure 2).

The study of risk factors for mortality revealed improved long-term prognosis for female patients (P=.005), those that did not have perioperative transfusions (P=.003), those that have had more than 15 adenopathies resected during the procedure (P=.004), and the administration of adjuvant treatment (P=.004). The multivariate study demonstrated that only transfusions and sex stood out as variables of interest. None of the histopathological variables studied were determinants in the evolution of the patient (Table 2). Lastly, we analysed patient distribution according to the borders of the resection and adjuvant treatment, with similar results. As such, 60% of patients with affected borders and 59% of patients with unaffected borders received concomitant treatment (n.s.). There were also no significant differences in long-term survival according to the analysis of the resected borders.

Discussion

Adenocarcinomas of the pancreas confer grim survival rates to patients in the studies published up until now, with similar statistics to those presented in this paper.[23,35-39] With this bleak prospective, the only treatment that has been shown to improve patient survival is surgery, with a highly debated contribution from chemotherapy and radiotherapy.[13,40,41]

Several different prognostic factors have been shown to influence survival in adenocarcinomas of the pancreas. These may include the biology of the tumour such as cellular differentiation,[42] cell ploidy,[43] microvascular density,[44] size of the lesion,[42,45] vascular invasion,[45,46] and lymphatic invasion at the moment of resection.[47,48] Regarding surgery, perioperative transfusions[45,42] and the hospital's experience[49,50] are variables that also influence the prognosis of the patient after intervention. However, the influence of these factors on survival during the perioperative period is not well known. Recently, the presence of postoperative complications has been correlated with reduced survival.[34,51] In our study, we have not been able to confirm these findings.

Transfusion of haemoderivatives and patient survival

The transfusion of haemoderivatives in the postoperative period after oncological surgery for colon cancer or liver metastases worsens the prognosis of the patient.[52] Various studies initially highlighted intraoperative blood loss as a prognostic factor in both univariate[19,53] and multivariate[39,51,54] analyses for pancreatic cancer surgery procedures. In addition to these findings, transfusions during the perioperative period was established as a factor to be taken into account in patient survival.[55] Therefore, both in older[56] and recent[55,57,58] studies, transfusions are marked as a negative factor. During the follow-up period, we found that 77% of the 141 transfused patients died, as opposed to 54% of the 53 patients that did not receive transfusions, which was a statistically significant difference. This appears to demonstrate that administering haemoderivatives also influences prognosis of pancreatic cancer. Meticulous technique during the procedure could imply less intraoperative haemorrhage, and this should be one of the top priorities for surgeons that specialise in treating these types of tumours.

The role of lymphadenectomy in long-term prognosis

In our experience, the resection of over 15 adenopathies was a factor that afforded increased survival in the univariate analysis, although this does not appear to be a definitive result, as the multivariate analysis ruled it out. On the other hand, Pawlik[48] demonstrated that the resection of over 15 adenopathies and the "ratio of resected/affected adenopathies" were important predictors of patient survival. Currently, however, controversy still exists on the benefit of extended lymphadenectomies. Published randomised studies have not been able to demonstrate differences when using extended lymphadenectomies.[19,26,42,59,60] Given the lack of unanimity in the medical opinion and lack of scientific evidence, we have opted to perform widened standard lymphadenectomies at our centre. As such, we include the retroperitoneal lymph nodes, and avoid performing lymphadenectomies around the celiac trunk and left border of the superior mesenteric artery. This technique, although it slightly increases the length of the surgery, does not appear to imply increased postoperative morbidity, by increasing the number of resected adenopathies, could provide increased patient survival according to some studies.[48]

Table 2 – Analysis of long-term mortality risk factors following a cephalic duodenopancreatectomy for pancreatic adenocarcinoma. The number of patients that died during the follow-up period in each category is displayed (No.), along with the percentage with respect to the total number of patients, according to the variable (%)

Variables		Long-term mortality			
		No.	%	Univariate analysis (P)	Multivariate analysis (P; OR [95% CI])
Sex	Male	92	73	.005	.01; 2.6 (1.1-5.9)
	Female	42	54		
Age, years	<70	101	70	n.s.	n.s.
	>70	33	58		
A.S.A.	I-II	92	66	n.s.	
	III	39	63		
ERCP	Yes	23	54	n.s.	
	No	109	69		
Surgical technique	CDPW	74	62	n.s.	
	CDPWR2	9	81		
	CDPPP	47	71		
	TP	4	50		
Venous resection	Yes	21	60	n.s.	
	No	113	70		
Wirsung	THIN	49	57	n.s.	
	THICK	47	68		
Pancreas	SOFT	37	61	n.s.	
	HARD	59	62		
Pancreaticojejunal anastomosis, pj	DM	67	62	.004	n.s.
	Non-DM	60	74		
Duration of the intervention, min	<360	50	65	n.s.	
	>360	67	64		
Complications	Yes	56	61	n.s.	
	No	78	69		
Transfusion during first 48 h	Yes	104	73	.003	.01; 2.9 (1.2-6.7)
	No	26	49		
Tumour size, mm	<30	83	61	n.s.	
	>30	49	70		
Invaded lymph node territory	loc	75	68	n.s.	
	reg	3	100		
	loc-reg	18	60		
Resected adenopathies	≤15	57	76	.004	n.s.
	>15	73	60		
Lymphatic permeation	Yes	93	67	n.s.	
	No	31	68		
Perineural invasion	Yes	98	63	n.s.	
	No	13	68		
Vascular invasion	Yes	48	64	n.s.	
	No	73	64		
Degree of tumour differentiation	mild	6	54	n.s.	
	moderate	78	60		
	severe	22	75		
Tumourous lymph nodes	Yes	95	66	n.s.	
	No	39	67		
Synchronous metastases	Yes	9	81	n.s.	
	No	125	65		
Invasion of resection borders	Yes	23	64	n.s.	
	No	111	66		
Invasion of the retroperitoneal borders (mesouncinate)	Yes	5	71	n.s.	
	No	125	67		
Invasion of the neck of the pancreas	Yes	9	81	n.s.	
	No	121	66		
Adjuvant treatment (yes/no)	Yes	75	66	.004	n.s.
	No	53	68		

CDPPP, cephalic duodenopancreatectomy with pyloric preservation; CDPW, cephalic duodenopancreatectomy with gastrectomy; CDPWR2, cephalic duodenopancreatectomy with gastrectomy and lymphadenectomy extended to the celiac trunk and superior mesenteric artery; CI, confidence interval; DM, ductal-mucosal; loc, local; loc-reg, local and regional; n.s., not significant; OR, odds ratio; TP, total pancreatectomy; reg, regional.

Adjuvant treatment in pancreatic cancer

The role of adjuvant treatment in pancreatic cancer continues to be a topic of discussion since the majority of available data from randomised clinical trials has insufficient statistical power, and even constitutes contradictory results. In the first studies by GITSG in 1985,[9] increased survival was demonstrated with chemotherapy based on 5-FU and radiotherapy, and this was established as standard adjuvant treatment in the United States. Subsequently, the EORTC[10] study confirmed these results with a tendency towards increased survival, although these results were not statistically significant. In 2001, the European study group ESPAC carried out the ESPAC-1 trial, in which they concluded that chemo-radiotherapy was ineffective and that all patients should receive adjuvant chemotherapy.[13] Recently, the CONKO-001 study demonstrated a much higher disease-free survival at 4 years in the group treated with gemcitabine as opposed to the control group.[61] Lastly, in the RTOG97-04 study, improvement was observed in the gemcitabine arm as opposed to the 5-FU arm in terms of median survival (20.6 months vs 16.9 months), as well as in 3-year survival (32% vs 21%; *P*=.03).[62] The results from these last two studies do not resolve the controversy regarding the optimal adjuvant treatment for pancreatic cancer. One could deduce that the treatment schemes based on gemcitabine represent the most favourable adjuvant treatment for patients with resected ADHP, and should serve as the basis for clinical trials designed in the future. Our study attests to the usefulness of adjuvant treatment in the univariate study on long-term survival.

Conclusion

In light of our results, we believe that oncologically complete surgery should include lymphadenectomies in the peripancreatic and retroperitoneal territories, and should be performed with low rates of morbidity[34] and without perioperative transfusions.

A broad consensus exists in the literature regarding the short- and long-term benefits of this surgery in high-volume health centres.[49,50,63-65] Indeed, some clinical guidelines only recommend performing this surgery in centres that practice over 20 CDP/year.[66-69] The creation of multidisciplinary teams at these centres is key for improving results in the treatment of patients with ADHP.[70]

In a recent editorial, Bradley[63] reflected on the concept of "healing" in pancreatic cancer, demarcating the difference between actual survival and actuarial survival with reference to this pathology. After reviewing all studies that reported actual survival results with a long follow-up period (5-10 years), this study indicated that only 177 and 51 patients, respectively, were still alive after surgery. This implies an actual survival rate less than 10% at 5 years and less than 3% after 10 years, similar to the results from our experience. Improved long-term results will probably depend on the development of more effective adjuvant treatments.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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